KINDLY AMEND THIS APPLICATION AS FOLLOWS:

In The Title:

Change the title of the invention to:

-- NUCLEIC ACID SEQUENCING PROCESSES USING NON-RADIOACTIVE DETECTABLE MODIFIED OR LABELED NUCLEOTIDES OR NUCLEOTIDE ANALOGS, AND OTHER PROCESSES FOR NUCLEIC ACID DETECTION AND CHROMOSOMAL CHARACTERIZATION USING SUCH NON-RADIOACTIVE DETECTABLE MODIFIED OR LABELED NUCLEOTIDES OR NUCLEOTIDE ANALOGS -- .

In The Abstract Of The Disclosure:

Substitute a new Abstract of the Disclosure attached hereto as Exhibit 1.

In The Claims:

Amend claims 569, 586, 587, 588, 600, 601, 602, 624, 713, 714, 716, 719, 720, 721, 738, 739, 740, 752, 753, 776, 859, 866, 868, 871, 872, 873, 890, 891, 892, 904, 905, 906, 928, 1011, 1012, 1017, 1018, 1020, 1023, 1024, 1025, 1042, 1043, 1044, 1056, 1057, 1058, 1164, 1169, 1170, 1172, 1175, 1176, 1177, 1281, 1291, 1297, 1298, 1340, 1349, 1405, 1409, 1411, 1430, 1432, 1434, 1435, 1448, 1468, 1471, 1473, 1474, 1475, 1476, 1499, 1507, 1565, 1566, 1570, 1582, 1608, 1624, 1628, 1632, 1639, 1647, 1686, 1687, 1688, 1696, 1699, 1700, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 1710, 1711, 1712, 1725 and 1726 as follows:

569. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactively labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

subjecting said detectable non-radioactively labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting non-radioactively the presence of each of said separated or resolved fragments by means of said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

586. (Twice Amended) The process according to claim 569, wherein the detectable non-radioactively labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

587. (Amended) The process according to claim 569, wherein said providing or generating step, the one or more non-radioactively modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

588. (Amended) The process according to claim 587, wherein at least one of said non-radioactively modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

600. (Amended) The process according to claim 569, wherein said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

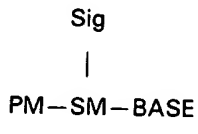
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

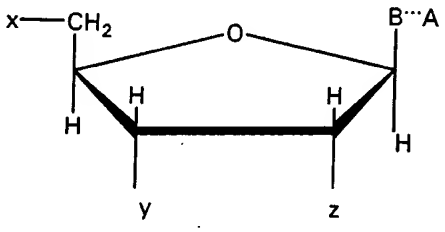
SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

601. (Amended) The process according to claim 569, wherein said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs have the structure:



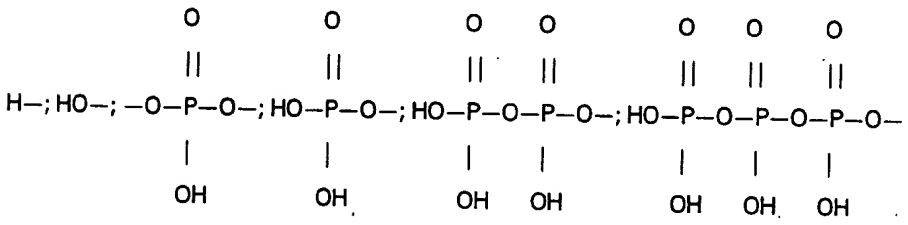
wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1' position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

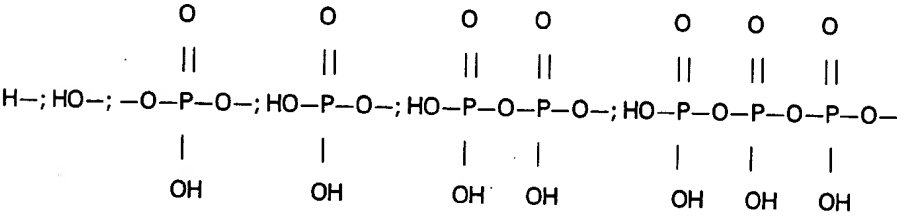
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H– and HO–.

602. (Amended) The process according to claim 601, wherein y and z [comprise] <u>are</u> H–.

624. (Amended) The process according to claim 621, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable <u>non-radioactive</u> signal.

713. (Amended) The process according to claim 709, wherein said detecting step is carried out by means of a directly detectable signal provided by said one or more non-radioactively modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

714. (Amended) The process according to claim 713, wherein in said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating compound, a fluorogenic compound, [a phosphorescent compound,] a chromogenic compound, a chemiluminescent compound and an electron dense compound.

716. (Twice Amended) The process according to claims 569, 600 or 601, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more non-radioactively modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

719. (Twice Amended) The process according to claim 569, wherein said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs are capable of being detected non-radioactively by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, [a phosphorescent measurement,] a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

720. (Amended) The process according to claim 569, wherein said detecting step comprises localizing said non-radioactively labeled nucleic acid fragments by means of said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs.

721. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactively labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

introducing or subjecting said detectable non-radioactively labeled fragments to a sequencing gel;

separating or resolving said fragments in said sequencing gel; and

detecting non-radioactively each of the separated or resolved fragments; and determining the sequence of said nucleic acid of interest.

738. (Twice Amended) The process according to claim 721, wherein the detectable non-radioactively labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

739. (Amended) The process according to claim 721, wherein said providing or generating step, the one or more non-radioactively modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

740. (Amended) The process according to claim 739, wherein at least one of said non-radioactively modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

752. (Amended) The process according to claim 721, wherein said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

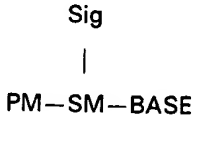
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

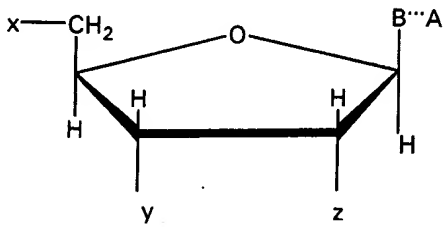
BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

753. (Amended) The process according to claim 721, wherein in said providing or generating step, the non-radioactively modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



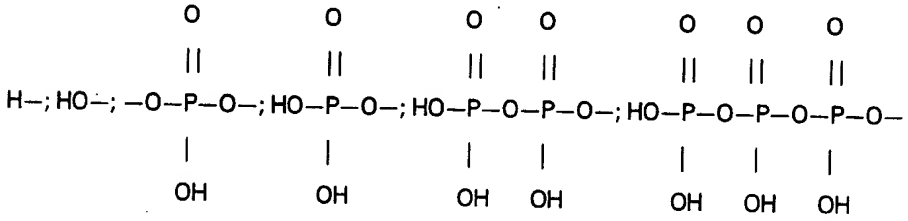
wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

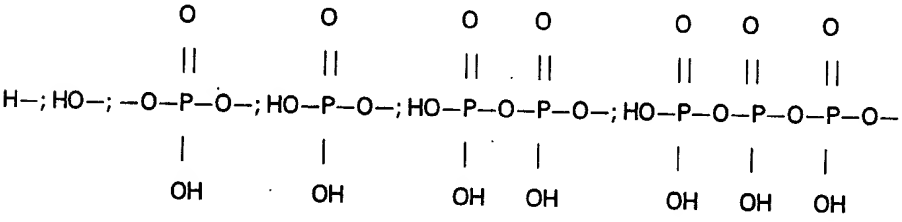
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H– and HO– .

754. (Amended) The process according to claim 753, wherein y and z [comprise] are [H] H– .

776. (Amended) The process according to claim 773, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

859. (Twice Amended) The process according to claim 721, wherein said detectable non-radioactively labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.

866. (Amended) The process according to claim 865, wherein in said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating compound, a fluorogenic compound, [a phosphorescent compound,] a chromogenic compound, a chemiluminescent compound and an electron dense compound.

868. (Amended) The process according to claims 721, 752 or 753, wherein said detecting step is carried out by means of a indirectly detectable signal provided by said one or more non-radioactively modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

871. (Twice Amended) The process according to claim 721, wherein said one or more modified or labeled nucleotides or nucleotide analogs are capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, [a phosphorescent measurement,] a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

872. (Twice Amended) The process according to claim 721, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs.

873. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof;

detecting non-radioactively the detectable non-radioactive labeled nucleic acid fragments with a sequencing gel; and

determining the sequence of said nucleic acid of interest.

890. (Twice Amended) The process according to claim 873, wherein the detectable non-radioactive labeled complementary nucleic acid is fragmented and separated prior to detecting in said sequencing gel.

891. (Amended) The process according to claim 873, wherein in said providing or generating step, the one or more non-radioactive modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

892. (Amended) The process according to claim 891, wherein at least one of said non-radioactive modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

904. (Amended) The process according to claim 873, wherein in said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

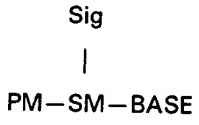
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

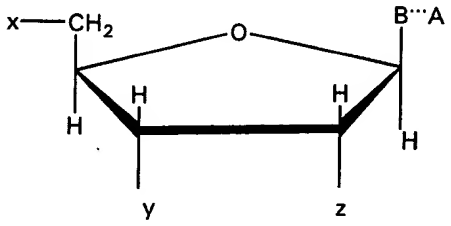
BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

905. (Amended) The process according to claim 873, wherein in said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



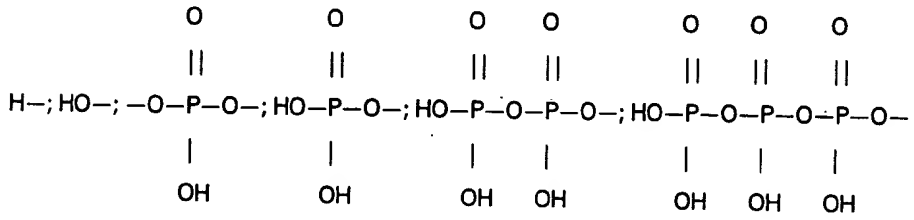
wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

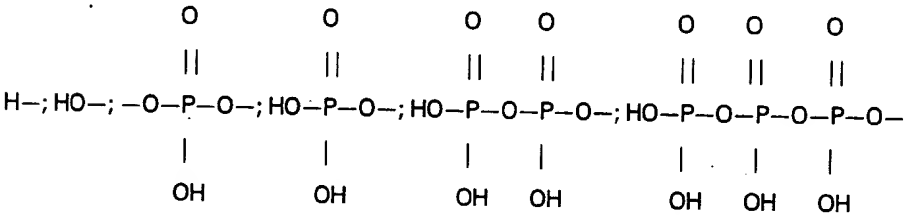
wherein B and A are covalently attached directly or through a linkage group,

wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H– and HO–.

906. (Amended) The process according to claim 905, wherein y and z [comprise] are [H] H– .

928. (Amended) The process according to claim 925, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

1011. (Twice Amended) The process according to claim 873, wherein said detectable non-radioactive labeled nucleic acid fragments are detectable by a non-radioactive means selected from the group consisting of a fluorescent measurement, a chemiluminescent measurement, and a combination thereof.

1012. (Twice Amended) The process according to claim 873, wherein said detecting step, the detectable non-radioactive labeled nucleic acid fragments are separated or resolved electrophoretically.

1017. (Amended) The process according to claim 1016, wherein said detecting step is carried out by means of a directly detectable signal provided by said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

1018. (Amended) The process according to claim 1013, wherein said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating compound, a fluorogenic compound, [a phosphorescent compound,] a chromogenic compound, a chemiluminescent compound and an electron dense compound.

1020. (Amended) The process according to claims 873, 904 or 905, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

1023. (Twice Amended) The process according to claim 873, wherein said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs are capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, [a phosphorescent measurement,] a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

1024. (Twice Amended) The process according to claim 873, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs.

1025. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting non-radioactively with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the base moiety or the base analog thereof.

1042. (Twice Amended) The process according to claim 1025, wherein the detectable non-radioactive labeled complementary nucleic acid is fragmented prior to separation in said sequencing gel.

1043. (Amended) The process according to claim 1025, wherein said providing or generating step, the one or more non-radioactive modified or labeled nucleotides or nucleotide analogs have been incorporated into said nucleic acid fragment or fragments.

1044. (Amended) The process according to claim 1043, wherein at least one of said non-radioactive modified or labeled nucleotides or nucleotide analogs is at a terminus of said fragment or fragments.

1056. (Amended) The process according to claim 1025, wherein said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more members selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

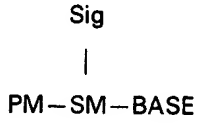
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

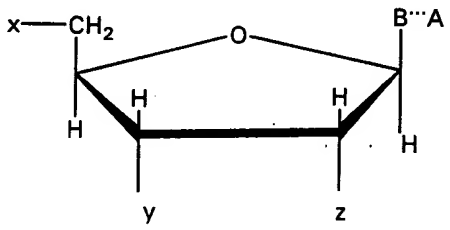
BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group.

1057. (Amended) The process according to claim 1025, wherein said providing or generating step, the non-radioactive modified or labeled nucleotides or nucleotide analogs have the structure:

(i)



wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

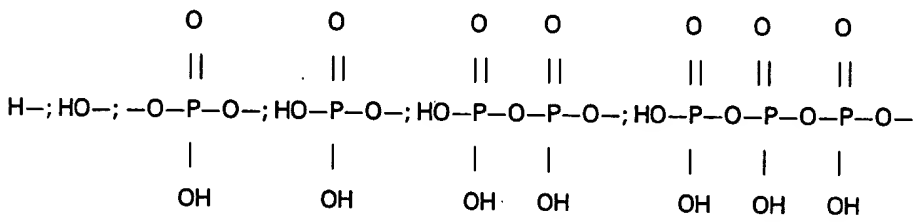
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group,

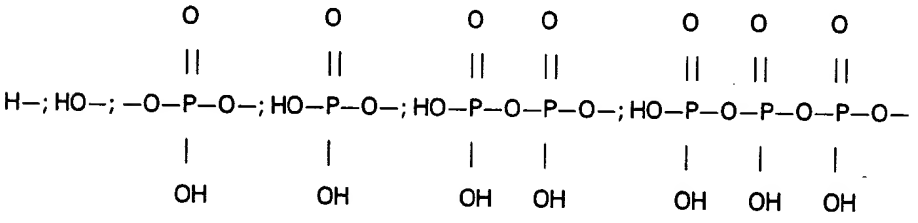
wherein if B is a purine or a purine analog, A is attached to the 8-position of the purine or purine analog, if B is a 7-deazapurine or 7-deazapurine analog, A is attached to the 7-position of the deazapurine or deazapurine analog, and if B is a

pyrimidine or a pyrimidine analog, A is attached to the 5-position of the pyrimidine or pyrimidine analog; and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H– and HO–.

1058. (Amended) The process according to claim 1057, wherein y and z [comprise] are [H] H– .

1164. (Twice Amended) The process according to claim 1025, wherein said detecting step, the detectable non-radioactive labeled nucleic acid fragments are separated or resolved electrophoretically.

1169. (Amended) The process according to claim 1165, wherein said detecting step is carried out by means of a directly detectable signal provided by said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

1170. (Amended) The process according to claim 1165, wherein said detecting step the directly detectable signal comprises a member selected from the group consisting of a chelating compound, a fluorogenic compound, [a phosphorescent compound,] a chromogenic compound, a chemiluminescent compound and an electron dense compound.

1172. (Amended) The process according to claims 1025, 1056 or 1057, wherein said detecting step is carried out by means of an indirectly detectable signal provided by said one or more non-radioactive modified or labeled nucleotides or nucleotide analogs, said A or said Sig detectable non-radioactive moiety.

1175. (Twice Amended) The process according to claim 1025, wherein said one or more modified or labeled nucleotides or nucleotide analogs are capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, [a phosphorescent measurement,] a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

1176. (Twice Amended) The process according to claim 1025, wherein said detecting step comprises localizing said detectable non-radioactive labeled nucleic acid fragments by means of said one or more modified or labeled nucleotides or nucleotide analogs.

1177. (Twice Amended) A process for determining with a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid of interest or a portion thereof, said process comprising the steps of:

(A) providing

(i) one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid; or

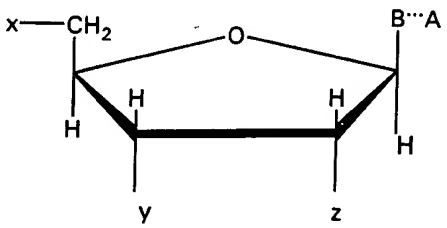
(ii) one or more oligonucleotides or polynucleotides comprising at least one said detectable non-radioactive chemically modified or labeled nucleotide or nucleotide analog; or

(iii) both (i) and (ii);

wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) and said oligonucleotides and polynucleotides (ii) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs have been modified or labeled non-disruptively or disruptively on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof; and;

(B) incorporating said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) or said one or more oligonucleotides or polynucleotides comprising at least one chemically modified or labeled nucleotides or nucleotide analogs (ii), or both (i) and (ii), into one or more nucleic acid fragments, to prepare detectable non-radioactive labeled fragments, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof and said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i)



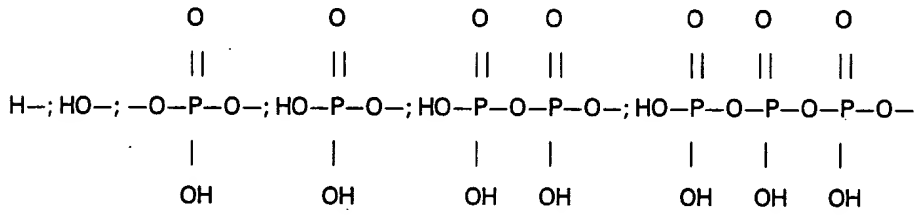
wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the

purine analog, the 7-deazapurine moiety or the 7-deazapurine analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

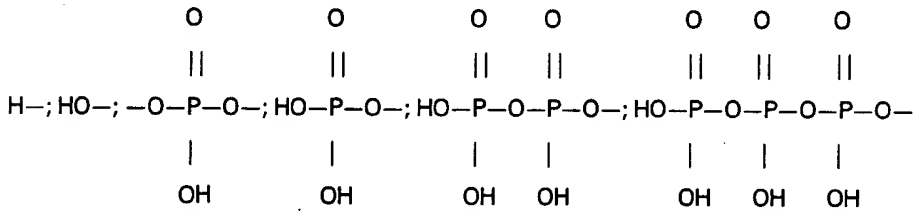
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety capable of producing directly or indirectly a detectable non-radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group, and

wherein x comprises a member selected from the group consisting of:

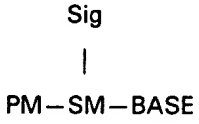


wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H– and HO– ;

(ii)



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said detectable non-radioactive labeled fragments to a sequencing gel;

(D) separating or resolving said detectable non-radioactive labeled fragments; and

(E) non-radioactively detecting directly or indirectly the presence of said detectable non-radioactive labeled fragments to determine the sequence of said nucleic acid of interest.

1281. (Twice Amended) The process according to claim 1177, wherein said detectable non-radioactive labeled nucleic acid fragment or fragments are terminally ligated or attached to a polypeptide.

1291. (Amended) The process according to claim 1290, wherein said detecting step the directly detectable signal providing A or Sig detectable non-radioactive moiety comprises a member selected from the group consisting of a fluorogenic compound, [a phosphorescent compound,] a chromogenic compound, a chemiluminescent compound and an electron dense compound.

1297. (Twice Amended) The process according to claim 1177, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, [a phosphorescent measurement,] a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

1298. (Twice Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(a) specifically hybridizing said nucleic acid of interest in the sample with one or more detectable non-radioactive labeled oligo- or polynucleotides, each such oligo- or polynucleotide being complementary to or capable of hybridizing with said nucleic acid of interest or a portion thereof, wherein said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

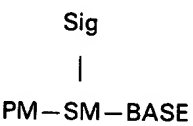
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

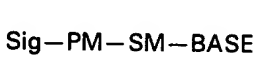
SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

(b) detecting non-radioactively the presence of said Sig detectable non-radioactive moieties in any of the detectable non-radioactive labeled oligo- or polynucleotides which have hybridized to said nucleic acid of interest.

1340. (Amended) The process according to claim 1298, wherein said covalent attachment in any of nucleotides (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

1349. (Amended) The process according to claim 1345, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

1405. (Amended) The process according to claim 1403, wherein said detecting step the directly detectable non-radioactive signal is provided by an enzyme.

1409. (Twice Amended) The process according to claim 1298, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, [a phosphorescent measurement,] a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

1411. (Twice Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(A) providing:

(i) an oligo- or polynucleotide [having two segments:

(a) a first segment] complementary to and capable of (1) specifically hybridizing to and forming a hybrid with a nucleic acid of interest or a portion thereof and (2) capable of binding to or complexing with a non-radioactively detectable protein [of said nucleic acid of interest; and

(b) a second segment comprising at least one protein binding nucleic acid sequence]; and

(ii) a non-radioactively detectable protein which is capable of binding to or complexing with said nucleic acid hybrid [protein binding nucleic acid sequence];

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said non-radioactively detectable protein (ii) to form a complex; and

(C) detecting non-radioactively the presence of said non-radioactively detectable protein in said complex [and] to detect said nucleic acid of interest.

1430. (Amended) The process according to claim 1411, wherein said oligo- or polynucleotide (i) comprises at least one protein binding nucleic acid sequence [is] selected from the group consisting of an antibody, a promoter, a repressor and an inducer.

1432. (Amended) The process according to claim [1411] 1430, wherein said at least one protein binding nucleic acid sequence is covalently attached to said oligo- or polynucleotide.

1434. (Amended) The process according to claim 1432, wherein said covalent attachment does not interfere substantially with the characteristic ability of said non-radioactively detectable protein to bind to any hybrid formed between said oligo- or polynucleotide (i) and said nucleic acid of interest.

1435. (Amended) The process according to claim 1432, wherein said covalent attachment does not interfere substantially with the characteristic ability of said non-radioactively detectable protein to be detected non-radioactively when bound to any hybrid formed between said oligo- or polynucleotide (i) and said nucleic acid of interest.

1448. (Amended) The process according to claim 1446, [Wherein] wherein said signaling component or indicator molecule comprises an aliphatic chemical moiety comprising at least four carbon atoms.

1468. (Amended) The process according to claims 1467, wherein said direct detection step is carried out by a member selected from the group consisting of a fluorogenic compound, [a phosphorescent compound,] a chromogenic compound, a chemiluminescent compound, an enzyme, a radioactive compound and an electron dense compound.

1471. (Twice Amended) The process according to claim 1411, wherein said nonradioactively detectable protein is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, [a phosphorescent measurement,] a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

1473. (Amended) A process for determining whether the number of copies of a particular chromosome in a cell is normal or abnormal, the process comprising the steps of:

contacting said cell under hybridizing conditions with one or more clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety or an analog of any of the foregoing thereof, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group,

to permit specific hybridization of said clone or clones or DNA fragments or oligo- or polynucleotides to the locus or loci of said particular chromosome;

detecting non-radioactively any specifically hybridized clone or clones or DNA fragments or oligo- or polynucleotides, and determining the number of copies of said particular chromosome; and

comparing said determined number of copies of said particular chromosome with a number of copies of said particular chromosome determined for a normal cell containing said particular chromosome, and determining whether the number of copies of said particular chromosome in said cell is abnormal.

1474. (Amended) A process for identifying a chromosome of interest in a cell containing other chromosomes, the process comprising the steps of:

providing a set of clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in said chromosome of interest, wherein said clones or fragments or said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

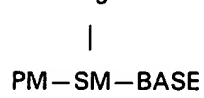
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said set of clones or DNA fragments or oligo- or polynucleotides, permitting specific hybridization of said set of clones or DNA fragments or oligo- or polynucleotides to said locus or loci in said chromosome of interest;

detecting non-radioactively any of said clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to said locus or loci in said chromosome of interest, and obtaining a pattern of hybridizations between said set of clones or DNA fragments or oligo- or polynucleotides and said chromosomes; and

identifying said chromosome of interest by means of said hybridization pattern obtained.

1475. (Amended) A process for identifying a plurality or all of the chromosomes in a cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein said clones or fragments or said oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci in a chromosome of said cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets are labeled with a different indicator molecule and each of said clones or DNA fragments or oligo- or polynucleotides comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotide or nucleotide analog are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

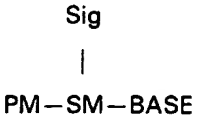
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to the locus or loci in said chromosomes; and

detecting non-radioactively any of said different indicator molecules in said sets of clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to the locus or loci in said chromosomes, and identifying any one of the chromosomes in said cell of interest.

1476. (Amended) A process for determining the number of chromosomes in an interphase cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments or oligo- or polynucleotides derived from said clones, wherein said set of clones or DNA fragments or oligo- or polynucleotides are specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest and each of said clones or DNA fragments or oligo- or polynucleotides in said sets comprises one or more detectable <u>non-radioactive</u> modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said <u>detectable non-radioactive</u> modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

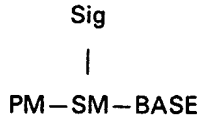
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety,

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is detectable non-radioactive moiety,

wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

contacting said interphase cell under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to any of the locus or loci in said chromosomes;

detecting non-radioactively any of said sets of clones or DNA fragments or oligo- or polynucleotides specifically hybridized to the locus or loci in said chromosomes, to obtain a pattern of generated signals; and comparing each generated signal with other generated signals in said pattern, and determining the number of chromosomes in said interphase cell of interest.

1499. (Amended) The process according to any of claims 1473, 1474, 1475 or 1476, wherein said covalent attachment in any of nucleotides (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

1507. (Amended) The process according to claim 1504, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

1565. (Amended) The process according to claim 1564, wherein said detecting step is carried out by means of a member selected from the group consisting of a fluorogenic compound, [a phosphorescent compound,] a chromogenic compound, a cherniluminescent compound and an electron dense compound.

1566. (Amended) The process according to claim 1564, wherein said detecting step the directly [-detectable] detectable non-radioactive signal is provided by an enzyme.

1570. (Twice Amended) The process according to any of claims 1473, 1474, 1475 or 1476, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, [a phosphorescent measurement,] a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

1582. (Twice Amended) A process for preparing a detectable non-radioactively labeled oligo- or polynucleotide of interest, comprising the steps of:

(A) providing either:

(1) one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA or an oligo- or polynucleotide of interest, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said other modified or unmodified nucleic acids are capable of incorporating into an oligo- or polynucleotide of interest, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs comprise one or more signaling moieties which are capable of providing directly or indirectly a detectable non-radioactive signal; or

(2) an oligo- or polynucleotide of interest comprising one or more said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides;

wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate moiety, the base moiety or the base analog, and are selected from the group consisting of:

(i)

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

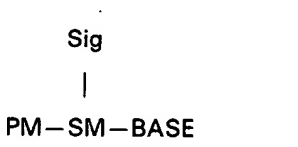
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii)



wherein

PM is a phosphate moiety or phosphate analog,

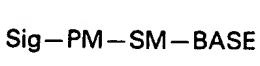
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a detectable non-radioactive moiety, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is detectable non-radioactive moiety; and

wherein PM is covalently attached to SM, BASE is covalently attached SM, and Sig is covalently attached to PM directly or through a linkage group;

provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

said oligo- or polynucleotide of interest; and

(B) either incorporating said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or polynucleotide, and preparing a non-radioactive labeled oligo- or polynucleotide of interest, or preparing said oligo- or polynucleotide of interest from said oligo- or polynucleotide recited in step (A)(2) above.

1608. (Amended) The process according to claim 1582, wherein said one or more detectable non-radioactive chemically modified nucleotides or said other modified or unmodified nucleic acids comprise a nucleoside di- or tri-phosphate.

1624. (Amended) The process according to claim 1623, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

1628. (Amended) The process according to claim 1627, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

1632. (Amended) The process according to claim 1631, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

1639. (Amended) The process according to claim 1582, wherein said covalent attachment in any of nucleotides (i), (ii) or (iii) does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

1647. (Amended) The process according to claim 1645, wherein said linkage group does not substantially interfere with formation of the signaling moiety or detection of the detectable non-radioactive signal.

1686. (Amended) The process according to claim 1582, wherein said Sig is detectable non-radioactively when the oligo- or polynucleotide is contained in a double-stranded ribonucleic or deoxyribonucleic acid duplex.

1687. (Amended) The process according to claim 1582, wherein said Sig is detectable non-radioactively when it is attached to the nucleotide directly or through a linkage group.

1688. (Amended) The process according to claim 1687, wherein said linkage group does not interfere substantially with the characteristic ability of Sig to form a detectable non-radioactive signal.

1696. (Amended) The process according to claim 1695, wherein said directly detectable signal providing Sig detectable non-radioactive moiety is selected from the group consisting of a fluorogenic compound, [a phosphorescent compound,] a chromogenic compound, a chemiluminescent compound, an electron dense compound and an enzyme.

1699. (Twice Amended) The process according to claim 1582, wherein said Sig detectable non-radioactive moiety is capable of being detected by a member selected from the group consisting of an enzymatic measurement, a fluorescent measurement, [a phosphorescent measurement,] a chemiluminescent measurement, a microscopic measurement and an electron density measurement.

1700. (Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

subjecting said labeled fragments to a sequencing gel to separate or resolve said fragments; and

detecting the presence of each of said separated or resolved fragments by means of the detectable radioactive signal provided by a radioactive metal chelated by said chelating compounds or chelating components in the detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

1701. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof;

introducing or subjecting said fragments to a sequencing gel;

separating or resolving said fragments in said sequencing gel; and

detecting each of the separated or resolved fragments by means of the detectable radioactive signal provided by a radioactive metal chelated by said chelating compounds or chelating components in the detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest.

1702. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the steps of:

providing or generating detectable non-radioactive labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof;

radioactively detecting with a sequencing gel the detectable non-radioactive labeled nucleic acid fragments [with a sequencing gel] by means of a radioactive metal chelated by said chelating compounds or chelating components; and

determining the sequence of said nucleic acid of interest.

1703. (Twice Amended) A process for determining the sequence of a nucleic acid of interest, comprising the step of detecting with a sequencing gel one or more detectable non-radioactive labeled nucleic acid fragments comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said one or more detectable non-radioactive modified nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the base moiety or the base analog thereof.

1704. (Twice Amended) A process for determining in a sequencing gel the presence of nucleic acid fragments comprising a sequence complementary to a nucleic acid sequence of interest or a portion thereof, said process comprising the steps of:

(A) providing

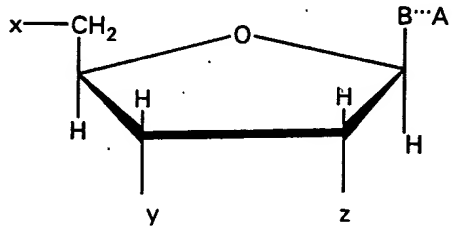
(i) one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into a nucleic acid, or

(ii) one or more oligonucleotides or polynucleotides comprising at least one of said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs; or

(iii) both (i) and (ii);

wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) and said oligonucleotides and polynucleotides (ii) are capable of attaching to or coupling to or incorporating into or forming one or more nucleic acid fragments, wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal, and wherein said detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs have been modified non-disruptively or disruptively on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety or the base analog thereof; and;

(B) incorporating said one or more detectable non-radioactive chemically modified or labeled nucleotides or nucleotide analogs (i) or said one or more oligonucleotides or polynucleotides comprising at least one of said detectable non-radioactive chemically modified or labeled nucleotides (ii), or both (i) and (ii), into said one or more nucleic acid fragments, to prepare detectable non-radioactive labeled fragments, each such fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, said detectable non-radioactive labeled fragments further comprising one or more detectable non-radioactive chemically modified nucleotides or nucleotide analogs selected from the group consisting of:

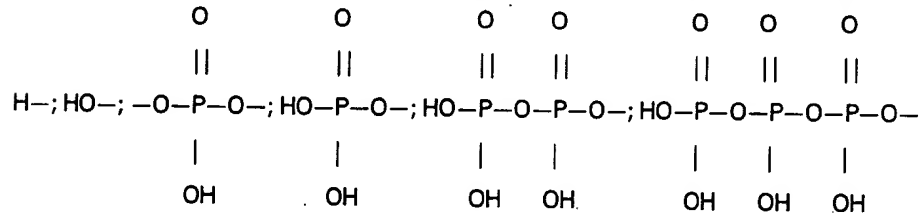


wherein B represents a purine moiety, a 7-deazapurine moiety, a pyrimidine moiety, or an analog of any of the foregoing, and B is covalently bonded to the C1'-position of the sugar moiety or sugar analog, provided that whenever B is a purine, a purine analog, a 7-deazapurine moiety or a 7-deazapurine analog, the sugar moiety or sugar analog is attached at the N9 position of the purine moiety, the purine analog, the, 7-deazapurine moiety or the 7-analog thereof, and whenever B is a pyrimidine moiety or a pyrimidine analog, the sugar moiety or sugar analog is attached at the N1 position of the pyrimidine moiety or the pyrimidine analog;

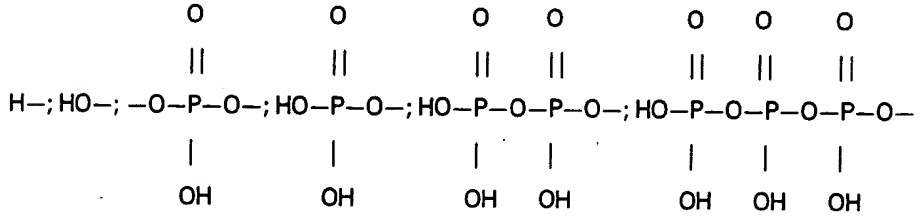
wherein A comprises at least three carbon atoms and represents at least one component of a signalling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing directly or indirectly a detectable radioactive signal; and

wherein B and A are covalently attached directly or through a linkage group, and

wherein x comprises a member selected from the group consisting of:



wherein y comprises a member selected from the group consisting of:



wherein z comprises a member selected from the group consisting of H- and HO- [--]

(ii)

Sig
|
PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, and

wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog,

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal; and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

(C) transferring or subjecting said labeled fragments to a sequencing gel;

(D) separating or resolving said labeled fragments; and

(E) detecting directly or indirectly the presence of said labeled fragments by means of a radioactive metal chelated by said chelating compounds or chelating components.

1705. (Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(a) specifically hybridizing said nucleic acid of interest in the sample with one or more oligo- or polynucleotides, each such oligo- or polynucleotide being complementary to or capable of hybridizing with said nucleic acid of interest or a portion thereof, wherein said oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

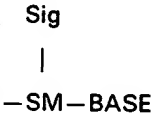
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety or a base analog of any of the foregoing; and

Sig is a signaling moiety comprising a chelating compound or component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

(ii) a nucleotide or nucleotide analog having the formula



wherein

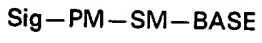
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or component capable of providing chelating a radioactive metal and a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or components capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, and such covalent attachment does not substantially interfere with double helix formation or nucleic acid hybridization;

provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal

oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and

(b) detecting radioactively the presence of said signaling moieties Sig in any of the oligo-or polynucleotides which have hybridized to said nucleic acid of interest by means of a radioactive metal chelated by said chelating compounds or chelating components.

1706. (Amended) A process for detecting a nucleic acid of interest in a sample, which process comprises the steps of:

(A) providing:

(i) an oligo- or polynucleotide having two segments:

(a) a first segment complementary to and capable of hybridizing to a portion of said nucleic acid of interest; and

(b) a second segment comprising at least one protein binding sequence; and

(ii) a detectable protein capable of binding to said protein binding sequence and comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal;

(B) contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide [(ii)] (i) and said detectable protein [(iii)] (ii) to form a complex;

(C) detecting radioactively the presence of said protein in said complex and said nucleic acid of interest by means of a radioactive metal chelated by said chelating compound or chelating component.

1707. (Twice Amended) A process for determining whether the number of copies of a particular chromosome in a cell is normal or abnormal, the process comprising the steps of:

contacting said cell under hybridizing conditions with one or more clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are capable of hybridizing specifically to a locus or loci of said particular chromosome or a portion thereof, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable non-radioactive modified or labeled nucleotides or nucleotide analogs , which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

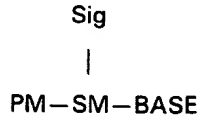
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety or an analog of any of the foregoing thereof, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

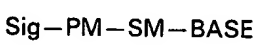
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group, to permit specific hybridization of said clone or clones or DNA fragments or oligo- or polynucleotides to the locus or loci of said particular chromosome;

detecting radioactively the signal generated by said specifically hybridized clone or clones or DNA fragments or oligo- or polynucleotides by means of a radioactive metal chelated by said chelating compound or chelating component, and determining the number of copies of said particular chromosome; and

comparing said determined number of copies of said particular chromosome with a number of copies of said particular chromosome determined for a normal cell containing said particular chromosome, and determining whether the number of copies of said particular chromosome in said cell is abnormal.

1708. (Amended) A process for identifying a chromosome of interest in a cell containing other chromosomes, the process comprising the steps of:

providing a set of clones or DNA fragments, or oligo- or polynucleotides derived from said clone or clones, wherein said clones or fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in said chromosome of interest, wherein said clones or fragments or oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotides or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

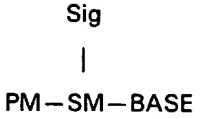
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of <u>chelating a radioactive metal and</u> providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said set of clones or DNA fragments or oligo- or polynucleotides, permitting specific hybridization of said set of clones or DNA fragments or oligo- or polynucleotides to said locus or loci in said chromosome of interest;

detecting radioactively by means of a radioactive metal chelated by said chelating compound or chelating component any signal generated by each of said clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to said locus or loci in said chromosome of interest, and obtaining a pattern of hybridizations between said set of clones or DNA fragments or oligo- or polynucleotides and said chromosomes; and

identifying said chromosome of interest by means of said hybridization pattern obtained.

1709. (Amended) A process for identifying a plurality or all of the chromosomes in a cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically hybridizable to a locus or loci in a chromosome of said cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets are labeled with a different indicator molecule and each of said clones or DNA fragments or oligo- or polynucleotides comprise one or more detectable modified or labeled nucleotides or nucleotide analogs capable of detection, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analogs are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

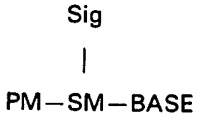
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a pyrimidine. or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog thereof;

(ii) a nucleotide or nucleotide analog having the formula



wherein

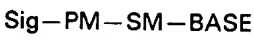
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a base moiety or base analog, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently

attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

fixing the chromosomes from or in said cell;

contacting said fixed chromosomes under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to the locus or loci in said chromosomes; and

detecting radioactively by means of a radioactive metal chelated by said chelating compound or chelating component any signal generated by each of said different indicator molecules in said sets of clones or DNA fragments or oligo- or polynucleotides which have specifically hybridized to the locus or loci in said chromosomes, and identifying any one of the chromosomes in said cell of interest.

1710. (Amended) A process for determining the number of chromosomes in an interphase cell of interest, the process comprising the steps of:

providing sets of clones or DNA fragments, or oligo- or polynucleotides derived from said clones, wherein each of said set of clones or DNA fragments or oligo- or polynucleotides are specifically complementary to or specifically hybridizable with at least one locus or loci in a chromosome of said interphase cell of interest, wherein each of said clones or DNA fragments or oligo- or polynucleotides in said sets comprise one or more detectable modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said modified or labeled nucleotide or nucleotide analog are selected from the group consisting of:

(i) a nucleotide or nucleotide analog having the formula

PM—SM—BASE—Sig

wherein

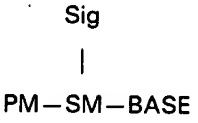
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine, or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE at a position other than the C5 position when BASE is a, pyrimidine moiety or a pyrimidine analog, at a position other than the C8 position when BASE is a purine or a purine analog, and at a position other than the C7 position when BASE is a 7-deazapurine or a 7-deazapurine analog;

(ii) a nucleotide or nucleotide analog having the formula



wherein

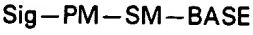
PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached SM directly or through a linkage group; and

(iii) a nucleotide or nucleotide analog, said nucleotide having the formula



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, wherein PM is covalently attached to the SM, BASE is covalently attached to SM, and Sig is covalently attached to PM directly or through a linkage group;

contacting said interphase cell under hybridizing conditions with said sets of clones or DNA fragments or oligo- or polynucleotides, and permitting specific hybridization of said sets of clones or DNA fragments or oligo- or polynucleotides to any of the locus or loci in said chromosomes;

detecting radioactively by means of a radioactive metal chelated by said chelating compound or chelating component any signals generated by each of said sets of clones or DNA fragments or oligo- or polynucleotides specifically hybridized to the locus or loci in said chromosomes, to obtain a pattern of generated signals; and comparing each generated signal with other generate signals in said pattern, and determining the number of chromosomes in said interphase cell of interest.

1711. (Amended) A process for preparing a labeled oligo- or polynucleotide of interest, comprising the steps of:

(A) providing either:

(1) one or more detectable chemically modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA or an oligo- or polynucleotide of interest, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides, wherein said other modified or unmodified nucleic acids are capable of incorporating into an oligo- or polynucleotide of interest, and wherein said chemically modified or labeled nucleotides or nucleotide analogs comprise one or more signaling

moieties comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, or

(2) an oligo- or polynucleotide of interest comprising one or more of said detectable chemically modified or labeled nucleotides or nucleotide analogs, alone or in conjunction with one or more other modified or unmodified nucleic acids selected from the group consisting of nucleotides, oligonucleotides and polynucleotides,

wherein said chemically modified or labeled nucleotides or nucleotide analogs are modified on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate moiety, the base moiety or the base analog, and are selected from the group consisting of:

(i)

PM—SM—BASE—Sig

wherein

PM is a phosphate moiety or phosphate analog,

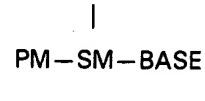
SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal, and

wherein PM is covalently attached to SM, BASE is covalently attached to SM, and Sig is covalently attached to BASE directly or through a linkage group at a position other than the C5 position when BASE is a pyrimidine moiety or an analog thereof, at a position other than the C8 position when BASE is a purine moiety or an analog thereof, and at a position other than the C7 position when BASE is a 7-deazapurine moiety or an analog thereof;

(ii)



wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a radioactive signal, and wherein said PM is covalently attached to SM, said BASE is covalently attached to SM, and Sig is covalently attached to SM directly or through a linkage group; and

(iii)

Sig—PM—SM—BASE

wherein

PM is a phosphate moiety or phosphate analog,

SM is a sugar moiety or sugar analog,

BASE is a pyrimidine, a purine or a 7-deazapurine base moiety, or a base analog of any of the foregoing, and

Sig is a signaling moiety comprising a chelating compound or chelating component capable of chelating a radioactive metal and providing a detectable radioactive signal; and wherein PM is covalently attached to SM, BASE is covalently attached SM, and Sig is covalently attached to PM directly or through a linkage group, provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3′ position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3′ terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide; and said oligo- or polynucleotide of interest;

and

(B) either incorporating said one or more modified or labeled nucleotides or nucleotide analogs (A)(1) into said oligo- or polynucleotide, and preparing a labeled oligo- or polynucleotide of interest, or preparing said oligo- or polynucleotide of interest from said oligo- or polynucleotide recited in step (A)(2) above.

1712. (Amended) A process for detecting the presence of a nucleic acid of interest in a sample, comprising the steps of:

providing or generating (i) one or more detectable non-radioactively labeled oligonucleotides or polynucleotides, each of said detectable non-radioactively labeled oligonucleotides or polynucleotides comprising a sequence sufficiently complementary to said nucleic acid of interest or to a portion thereof to specifically hybridize [thereto] therewith, wherein said one or more detectable non-radioactively labeled oligonucleotides or polynucleotides comprise one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogues, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA, and wherein said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof, and (ii) a sample that may contain said nucleic acid of interest;

forming in liquid phase hybrids comprising said one or more detectable non-radioactively labeled oligonucleotides or polynucleotides [and] specifically hybridized with said nucleic acid of interest;

separating or resolving in a gel said formed hybrids; and

detecting non-radioactively the separated or resolved hybrids to detect the presence of said nucleic acid of interest.

1725 (Amended) The process according to claim 1400, wherein said [direction] direct detection is carried out with the same indicator molecules.

1726. (Amended) The process according to claim 1400, wherein said [direction] direct detection is carried out with different indicator molecules.

* * * * * * *

REMARKS

Reconsideration of this application is respectfully requested.

Claims 569-717, 719-869, 871-1021, 1023-1173, 1175-1294, 1296-1407, 1409-1568, 1570-1612 and 1614-1727 were previously pending in this application. Claims 569, 586-588, 600-602, 624, 713-714, 716, 719-721, 738-740, 752-753, 776, 859, 866, 868, 871-873, 890-892, 904-906, 928, 1011-1012, 1017-1018, 1020, 1023-1025, 1042-1044, 1056-1058, 1164, 1169-1170, 1172, 1175-1177, 1281, 1291, 1297-1298, 1340, 1349, 1405, 1409, 1411, 1430, 1432, 1434-1435, 1448, 1468, 1471, 1473-1476, 1499, 1507, 1565-1566, 1570, 1582, 1608, 1624, 1628, 1632, 1639, 1647, 1686-1688, 1696, 1699-1712 and 1725-1726 have been amended. No claims have been added or canceled. Accordingly, claims 569-717, 719-869, 871-1021, 1023-1173, 1175-1294, 1296-1407, 1409-1568, 1570-1612 and 1614-1727 as amended hereinabove are presented for further prosecution on the merits.

Applicants and their attorney appreciate the time and courtesy extended to them by Examiner Ardin H. Marschel at the interview held on December 5, 2000 at the U.S. Patent and Trademark Office.

A new title of the invention and abstract of the disclosure have been substituted. Attached to this Amendment as Exhibit 1, the new abstract is believed to be more descriptive of the present invention and in conformance with the Manual of Patent Examining Procedure (MPEP) §608.01(b) [Guidelines For The Preparation Of Patent Abstracts, pages 600-51 and 600-52]. As such, the new abstract should enable the reader to ascertain quickly the character of Applicants' subject matter covered by their disclosure, including that which is new in the art to which the present invention pertains.

In a sincere effort to clarify their claimed invention and to facilitate examination of their application, Applicants have made a number of amendments to the claims. Among the clarifying amendments are those to the sequencing claims involving the insertion of the term "non-radioactive" before "labeled nucleic acid fragments" and "modified or labeled nucleotides or nucleotide analogs" in claims 569, 721, 873, 1025 and 1177, all of which are independent. The word

"detectable" has also been inserted variously into these claims. In claim 1177, the last step (E) has been amended to recite "non-radioactively detecting directly or indirectly the presence of said detectable non-radioactive labeled fragments to determine the sequence of said nucleic acid of interest."

Further, "non-radioactive"or similar terminology has been added to several dependent sequencing claims, including claims 586-588, 600-601, 624, 713, 716, 719, 720, 738-740, 752-753, 776, 859, 868, 872, 890-892, 904-905, 928, 1011-1012, 1017, 1020, 1023-1024, 1042-1044, 1056-1057, 1164, 1169, 1172, 1176 and 1281. With respect to other dependent sequencing claims, the word "is" has been substituted for "comprises" in claims 602, 754, 906 and 1058. Furthermore, the element "phosphorescent" as recited in various Markush claims has been deleted altogether. The affected Markush sequencing claims include claims 714, 719, 866, 871, 1018, 1023, 1170, 1175, 1291 and 1297.

Subject matter drawn to detection processes has also been amended. Claim 1298 have been amended by inserting the word "non-radioactive" or similar terminology before "oligo- or polynucleotides" and "modified or labeled nucleotides or nucleotide analogs." Nucleotide or nucleotide analogs (iii) have also been further defined in the first step (a) of claim 1298. There, proviso language has been added to the effect "that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide." The genesis of this language is found in the original specification, page 53, first full paragraph. There, Applicants disclose:

> Broadly, in another aspect of the practices of this invention various methods are useful for the tagging or labeling of DNA in a non-disruptive manner. For example, ***biotin is added on the end of a DNA or RNA molecule. The addition of biotin is accomplished by addition of a ribonucleotide. The 3',4' vicinal hydroxyl groups are oxidized by periodate oxidation*** and then reduced by a borohydride in the presence of biotin hydrazide. Alternatively, carbodiimide can also be used to couple biotin to the aldehyde group.
>
> [emphasis added]

Like claim 1298, claim 1411 is an independent claim directed to a process for detecting a nucleic acid of interest. Each of the three steps in claim 1411 have been amended. The first step (A) has been amended to read "providing: (i) an oligo- or polynucleotide complementary to and capable of (1) specifically hybridizing to and forming a hybrid with a nucleic acid of interest or a portion thereof and (2) capable of binding to or complexing with a non-radioactively detectable protein; and (ii) a non-radioactively detectable protein which is capable of binding to or complexing with said nucleic acid hybrid. Step (B) now recites "contacting a sample suspected of containing said nucleic acid of interest with said oligo- or polynucleotide (i) and said non-radioactively detectable protein (ii) to form a complex." The third step (C) in claim 1411 now reads "detecting non-radioactively the presence of said non-radioactively detectable protein in said complex to detect said nucleic acid of interest.

In accordance with the changes to claim 1411, claims 1430 and 1432 have also been amended. The former has been changed to read "[t]he process according to claim 1411, wherein said oligo- or polynucleotide (i) comprises at least one protein binding nucleic acid sequence selected from the group consisting of an antibody, a promoter, a repressor and an inducer." As amended above, the latter claim now recites "[t]he process according to claim1430, wherein said at least one protein binding nucleic acid sequence is covalently attached to said oligo- or polynucleotide."

As in the case of the sequencing claims discussed *supra*, dependent detection process claims have also been similarly amended. "Non-radioactive" or similar terminology has been inserted in claims 1340, 1349, 1405 and 1434-1435. Various Markush claims have been amended by deleting "phosphorescent" as an element. These Markush claims include claims 1409, 1468 and 1471. A minor error in claim 1448 with respect to the inadvertent capitalization of "Wherein" has also been corrected.

Chromosomal characterization claims have received similar treatment as the detection processes. The independent claims drawn to process for chromosomal characterization, 1473-1476, have been amended by adding the phrases "non-radioactive" or "detectable non-radioactive" in the first step of each claim. In three dependent claims 1499, 1507 and 1566, the term "non-radioactive" or "detectable

non-radioactive" has been inserted before "signal." The term "a phosphorescent compound" has also been deleted from the Markush members of claim 1565. Similarly, "a phosphorescent measurement" has been expunged from the Markush members of claim 1570.

Claim 1582 has been amended above. Drawn to a process for preparing a detectable non-radioactively labeled oligo- or polynucleotide of interest, this claim has been amended by inserting "non-radioactive" or "detectable non-radioactive" in several instances. The proviso language for nucleotide or nucleotide analog (iii), discussed *supra*, with respect to detection process claim 1298 has also been added to claim 1582. Claims depending from claim 1582 have been amended with respect to "non-radioactive" and "detectable non-radioactive" (claims 1608, 1624, 1628, 1632, 1639, 1647, 1686 and 1687-1688). In claim 1696, "a phosphorescent compound" has been deleted. In a similar fashion, "a phosphorescent measurment" has been removed from claim 1699. Both claims are written in Markush format.

Several claims are directed to the chelating aspects of Applicants' claimed invention and these have also been amended. Claims 1700-1704 are directed to sequencing processes using chelators which provide a radioactive signal. Each of these five claims have been amended by inserting the terms "non-radioactive" or "detectable non-radioactive" therein. Further, the one or more chelating compounds or components are now defined as "capable of chelating a radioactive metal and providing a non-radioactive signal." Even further, claims 1700-1702 and 1704 define detecting as being carried out "by means of the detectable radioactive signal provided by a radioactive metal chelated by said chelating compounds or chelating components in the detectable non-radioactive modified or labeled nucleotides or nucleotide analogs." Claim 1703 has been amended to recite "wherein said detectable non-radioactive modified or labeled nucleotides or nucleotide analogs comprise one or more chelating compounds or chelating components capable of chelating a radioactive metal and providing a detectable radioactive signal."

Claim 1705 is directed to a detection process using one or more chelating compounds or components. This independent claim has been amended by the insertion of the terms "non-radioactive" or "detectable non-radioactive." Further,

the chelating compounds or components are defined as being capable of "chelating a radioactive metal and providing a detectable radioactive signal." Moreover, the proviso language with respect to "vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide," discussed *supra*, has been added to the nucleotide or nucleotide analogs (iii) in claim 1705. Finally, the last step of detecting in claim 1705 has been changed to read "detecting radioactively the presence of said signaling moieties Sig in any of the oligo- or polynucleotides which have hybridized to said nucleic acid of interest by means of a radioactive metal chelated by said chelating compounds or chelating components."

Claim 1706 is also an independent and is directed to a detection process. Related to claim 1411, this claim has been amended by inserting "detectable" before "protein" (ii) and further clarifying that the chelating compound or component is capable of "chelating a radioactive metal . . ." Two minor errors in the contacting step (B) of claim 1706 have been corrected, "(i)" and "ii" now being properly recited. As in the case of detection process claim 1705, the last step of detecting in claim 1706 has been amended to recite "detecting radioactively the presence of said protein in said complex and said nucleic acid of interest by means of a radioactive metal chelated by said chelating compound or chelating component."

Claims 1707-1710, counterparts to chromosomal characterization claims 1473-1476, are directed to processes involving chelating compounds or chelating components and radioactive detection. Claims 1707-1710 have been amended with respect to inserting "non-radioactive" and "detectable non-radioactive," clarifying that the chelating compound or chelating component is capable of "chelating a radioactive metal," and detecting "by means of a radioactive metal chelated by said chelating compounds or chelating components."

Claim 1711 is a process for preparing a labeled oligo- or polynucleotide of interest involving chelating compounds or chelating components. As in the case of claim 1705, also a chelating claim but for a detection process, proviso language with respect to "vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide," discussed *supra*, has been added to the nucleotide or nucleotide analog (iii) in claim 1711. Minor clarification has

also been made in claim 1711 with respect to "detectable chemically modified or labeled nucleotides or nucleotide analogs" and the chelating compound or chelating component being capable of "chelating a radioactive metal."

Claim 1712 is directed to a process for detecting nucleic acids of interest involving the formation of liquid phase hybrids. In this claim, clarification has been made with respect to "non-radioactive" oligonucleotides or polynucleotides, and "non-radioactive" modified or labeled nucleotides or nucleotide analogs. Further, the non-radioactively labeled oligonucleotides or polynucleotides are defined as "comprising a sequence sufficiently complementary to said nucleic acid of interest or a portion thereof to specifically hybridize therewith . . ." The second forming step has also been amended and now reads that hybrids are formed "comprising said one or more detectable non-radioactively labeled oligonucleotides or polynucleotides specifically hybridized with said nucleic acid of interest. The last step of detecting has also been clarified to recite "detecting non-radioactively the separated or resolved hybrids to detect the presence of said nucleic acid of interest."

Lastly, informalities with respect to claims 1725 and 1726 have been corrected. In both claims, the phrase "direction detection" has been changed to -- direct detection. --

Most if not all of the above amendments to the claims have been made in an effort to clarify Applicants' claimed invention by adopting the Examiner's suggestions or meeting his requirements for claim clarity. Entry of the above amendments is respectfully requested.

Applicants appreciate the indication in the January 30, 2001 Office Action (page 2) that rejections and/or objections not reiterated from previous office actions have been withdrawn and that the three rejections in the latest action constitute the complete set presently being applied against the present application.

The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 569-717, 719-869, 871-1021, 1023-1173, 1175-1294, 1296-1407, 1409-1568, 1570-1612, and 1614-1727 stand rejected for indefiniteness under 35 U.S.C. §112, second paragraph. In the Office Action (pages 2-5), the Examiner stated:

> **[1]** It is noted that the instant disclosure is directed to the preparation and use of nucleotide analogs wherein they are labeled or modified in their chemical structure so as to be nonradioactively detectable. Radioactive analogs are also described, especially in the reference which is incorporated by reference to Ward et al. (P/N 4,711,955) wherein radioactive elements are present in prior art labeled nucleic acids. The replacement of such radioactive nucleotide labels with nonradioactive alternatives is extensively summarized in columns 13. Numerous biotinylated nucleotides and corresponding nucleic acid polymers are described in said Ward et al. as well as in the instant application wherein numerous nucleotide analogs and polynucleotides are described. Consideration of the entirety of these two disclosures, however has failed to reveal preparatory or use descriptions for the inventions therein described wherein the labeling includes both radioactive and non-radioactive means, except for a specific set of embodiments directed to chelating a radioactive metal. It is noted that even the chelating groups per se are non-radioactive. Only the metal gives radioactivity to the label. Metals are listed in the instant specification as filed on page 85. No other radioactive labeling is described as to its preparation or use in the instant disclosure. It is noted that all of the independent claims that are presently pending fail to limit the invention to non-radioactively labeled nucleotide practice and thus the claims are not commensurate in scope with the specification, especially because double modification is only disclosed in the radioactive metal-chelator embodiments. For example, in claim 569, lines 3-11, the nucleic acid fragments therein are detectable and labeled and are optionally described as modified or as analogs. Then in the last three lines of claim 569 they are detected non-radioactively. Thus, these two sections of the claim differ in scope in that the lines 3-11 are inclusive of a wide variety of labeled or modified nucleotide practice whereas in contrast only non-radioactive detection is performed in the last 3 lines. It is noted that radioactive detection is disclosed wherein chelated radioactive metal is present in the nucleic acid probe. Thus unclarity pertains to claims 569-717, 719-869, 871-1021, 1023-1173, 1175-1294, 1296-1407, 1409-1568, 1570-1612, 1614-1699, and 1712-1727. Clarification is requested via clearer claim wording.

Continuing on pages 4-5 in the Office Action, the Examiner further stated:

[2] Claims 1700-1711 are vague and indefinite for a similar reason as the above claims. In these claims chelating nucleotide analogs are described but without clarifying the radioactive presence as being in the metal that is chelated. For example, in claim 1700, lines 3-13, chelating compounds or components are described but without indicating the presence or absence of a radioactive metal. It is noted that chelating compounds or components do not necessarily actually contain a chelated metal. They may be and usually are prepared without the metal presence which is only added later during a radioactive labeling step. Clarification via clearer claim wording is requested in order to clearly word the claims to correspond to the chelating-metal practice in the specification.

[3] Claims 1712-1718 and 1727 are additionally vague and indefinite in that these claims are directed to detecting a nucleic acid of interest but do not contain any specificity of hybridization. Also, the last line of the claim lacks any indication that the resolved hybrids only contain the nucleic acid of interest hybridized to the labeled oligonucleotide or polynucleotide as an indication of detecting the presence of the nucleic acid of interest. Clarification is requested via clearer claim wording as to some type of specificity which results in actual nucleic acid of interest detection.

[4] Claim 602 is vague and indefinite in that moieties y and z are indicated as either being H— or HO— whereas claim 602 also indicates open claim language via the word "comprise" in line 2. It is unclear what additionally would be present in y or z to correspond to the open word "comprise". Claims 754, 906, and 1058 also contain this unclarity.

In order to ensure that each and every point in the indefiniteness rejection has been addressed, Applicants' attorney has taken the liberty of inserting bold bracketed numbers in front of each of the four issues. The remarks below are directed to the four issues as designed by bold bracketed numbers.

[1] As indicated in the opening remarks of this paper, a number of claims have been amended with respect to the non-radioactive nature of the nucleic acid fragments or oligo- or polynucleotides. The amended claims include the following:

Independent Claim Number	Dependent Claim Number(s)	Amendment/Language
569		non-radioactively
		detectable non-radioactively
	586-588	non-radioactively
	600-601	non-radioactively
	624	non-radioactive
	713, 716	non-radioactively

Independent Claim Number	Dependent Claim Number(s)	Amendment/Language
	719	detectable non-radioactively
	720	non-radioactively
		detectable non-radioactively
721		non-radioactively
		detectable non-radioactively
	738-741	non-radioactively
	752-753	non-radioactively
	776	non-radioactive
	859, 868	non-radioactively
	872	non-radioactive
873		non-radioactive
		detectable non-radioactive
	890-892	non-radioactive
	904-905	non-radioactive
	928, 1011-1012	non-radioactive
	1017, 1020,	non-radioactive
	1023-1024	non-radioactive
1025		non-radioactive
		detectable non-radioactive
	1042-1044	non-radioactive
	1056-1057	non-radioactive
	1164, 1169	non-radioactive
	1172, 1176	non-radioactive
1177		non-radioactive
		detectable non-radioactive
	1281	non-radioactive
1298		non-radioactive labeled
		non-radioactive
		detectable non-radioactive
	1340, 1349, 1405	non-radioactive
1411		non-radioactively detectable
		non-radioactively
	1434-1435	non-radioactively
1473-1476		non-radioactive

Independent Claim Number	Dependent Claim Number(s)	Amendment/Language
		detectable non-radioactive
	1499, 1507	non-radioactive
	1566	detectable non-radioactive
1582		non-radioactive
		detectable non-radioactive
		detectable non-radioactive chemically
	1608	detectable non-radioactive
	1624, 1628, 1632	non-radioactive
	1639, 1647	non-radioactive
	1686-1687	non-radioactively
	1688	non-radioactive
1700-1711		non-radioactive
		detectable non-radioactive
		chelating a radioactive metal
		a radioactive metal chelated by
1712		non-radioactively labeled
		detectable non-radioactively
		to detect the presence of said nucleic acid of interest

As seen in the list above, the claims at hand have been amended to limit Applicants' invention to non-radioactively labeled nucleotide practice. Further, with respect to the radioactive metal-chelator embodiments, detection is now defined as being carried out "by means of the detectable radioactive signal provided by a radioactive metal chelated by said chelating compounds or chelating components . . ." It is believed that the above-listed amendments to the claims clarifies Applicants' invention in regard to both non-radioactively labeled nucleotidyl practice and radioactive metal-chelator practice so that the recited detection is commensurate with the modification or labeling undertaken for each process being claimed.

[2] As seen in the claim amendments and as discussed in the opening remarks of this paper as well as in the immediately preceding paragraph, Applicants have amended each of claims 1700-1711 to define detection as being carried out "by means of the detectable radioactive signal provided by a radioactive metal chelated by said chelating compounds or chelating components . . ." It is believed that the amendments to claims 1700-1711 clarifies the claim wording to correspond to the chelating-metal practice disclosed in the specification at hand.

[3] As noted earlier, the specificity of hybridization has been added to claim 1712. In the first providing or generating step of claim 1712, the detectable non-radioactively labeled oligonucleotides or polynucleotides comprise "a sequence sufficiently complementary to said nucleic acid of interest or to a portion thereof to specifically hybridize therewith, . . ." Further, the second formation step in claim 1712 calls for forming "hybrids comprising said one or more detectable non-radioactively labeled oligonucleotides or polynucleotides specifically hybridized with said nucleic acid of interest. Because claims 1713-1718 and 1727 depend from claim 1712 which has been amended to contain the requisite specificity of hybridization, it is believed that these claims have been properly clarified.

[4] As indicated earlier, each of claims 602, 754, 906 and 1058 has been amended by deleting the word "comprise" in favor of -- are -- . Thus, each claim recites "wherein y and z are H— ."

In view of the above amendments to the claims and the foregoing remarks directed to the four issues [1] through [4], Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

The Rejection Under 35 U.S.C. §102(b)

Claims 1298-1302, 1304, 1306, 1320, 1327-1333, 1336-1340, 1342-1343, 1345-1350, 1352-1353, 1355, 1358-1360, 1371, 1373-1374, 1385-1386, 1388-1394, 1396, 1398-1400, 1403-1404, 1406-1407, 1409-1410, 1582-1583, 1601, 1612, 1614-1618, 1622, 1627-1639, 1641-1642, 1644-1648, 1650-1651, 1653, 1656-1658, 1662, 1669, 1671-1672, 1677, 1682, 1684, 1686-1690, 1692, 1694-1699, 1705, 1711, and 1725 stand rejected under 35 U.S.C. §102(b) for anticipation by Broker et al. ["Electron microscopic visualization of tRNA genes with ferritin-avidin: biotin labels," Nucleic Acids Research 5(2):363-384 (1978)]. In the Office Action (pages 5-6), the Examiner stated:

> Broker et al. discloses the incorporation of biotin onto a 3' terminus of a tRNA via a diamino alkyl bridge as summarized in the abstract which is then utilized to hybridize to phage DNA. The hybrid is visualized in Figure 5 on page 377 in a nonradioactive manner via ferritin. The 3'terminal labeling may be viewed either as sugar moiety labeling or phosphate moiety labeling of the penultimate nucleotide in the tRNA. It is additionally noted that the incorporation of this label is performed in the EXPERIMENTAL PROCEDURES via 3' modification of the tRNA and thus incorporated in parts. The instant claims, however, do not limit the manner of incorporation thus supporting the anticipation of the instant claims as listed above.

As indicated above, claims 1298, 1582, 1705 and 1711 have each been amended with respect to the 3' terminal labeling of the sugar or phosphate moiety. As now defined, the phosphate moiety labeled nucleotide or nucleotide analog (iii) in these four claims contain the following proviso language:

> provided that when said nucleotide or nucleotide analog (iii) is attached to an oligoribonucleotide or a polyribonucleotide, and provided that when Sig is attached through a chemical linkage to a terminal PM at the 3' position of a terminal ribonucleotide, said chemical linkage is not obtained through a 2',3' vicinal oxidation of a 3' terminal ribonucleotide previously attached to said oligoribonucleotide or polyribonucleotide.

It was noted in the opening remarks of this paper (page 70, second full paragraph) that support for the above-recited language is taken from the specification, page 53, first full paragraph. The remaining claims which were rejected for anticipation are all believed to rest ultimately upon claims 1298, 1582,

1705 and 1711 which have been amended to eschew the vicinal oxidation chemistry disclosed in the cited Broker et al. article - at least for the nucleotides or nucleotide analogs modified or labeled on the phosphate moiety.

With respect to the sugar moiety labeling set forth in the rejection, it is believed that a proper analysis of Broker's chemistry would lead one of ordinary skill in the art to infer – at the most and if at all – that it was the previous phosphate moiety upstream that was now carrying a label – and not the previous sugar moiety. In support of the foregoing position, Applicants offer the following remarks. **First**, Applicants' claimed invention is centrally directed to the non-radioactive modification of nucleotides and nucleotide analogs for use in detection and preparation processes. Such nucleotides and nucleotide analogs are generally modified so as to attach a detectable signaling moiety (Sig) to one of the defined elements of the nucleotide or nucleotide analog – be it the base moiety or base analog, the sugar moiety or sugar analog, or the phosphate moiety or phosphate analog. In the case of Broker's chemistry, the terminal nucleotide in the tRNA is literally disemboweled, necessitating the characterization that what is left behind after the terminal sugar is oxidized and literally ripped open must be a linker arm to the previous nucleotidyl moiety. Thus, in the case of Applicants' modified or labeled nucleotides or nucleotide analogs, a positive step of placing a detectable non-radioactive Sig moiety is carried out. In Broker's chemistry, no such positive step is carried out. Rather, a negative step of breaking apart the terminal ribonucleotide in the tRNA is undertaken. **Second**, assuming *arguendo*, that what is left behind in Broker's chemistry constitutes a linker arm to the previous nucleotidyl element, the only logical and reasonable candidate would be the previous nucleotide, which would inevitably lead the ordinarily skilled artisan to believe that it was the phosphate moiety of the penultimate nucleotide that was now connected to the linker arm effected through Broker's chemistry. It is quite clear that the base moiety is certainly not being labeled. And when one views the nucleotidyl structure as a whole, then the sugar moiety would also not be viewed as being labeled by Broker's chemistry because that analysis would require one to accept that the phosphate moiety of the penultimate nucleotide is a linker arm itself. In this regard, Applicants have attached the structure for a ribonucleotide as Exhibit 2. As indicated by Arrow A (Exhibit 2), the 3' terminal sugar is oxidized and split open. As shown by Arrow B (Exhibit 2), the phosphate moiety which is part of the penultimate nucleotide is clearly attached to the structure that remains after

Broker's chemistry is carried out. As shown by Arrow C (Exhibit 2), to say that it is the sugar moiety of the penultimate nucleotide being labeled by Broker's chemistry would require one to classify and to characterize the phosphate moiety of the penultimate nucleotide as a linker arm itself. That is contrary to convention in the art and contrary to Applicants' disclosure. Applicants have not described the phosphate moiety as a linker arm because it is clearly a separate nucleotidyl element in and of itself, just as the base moiety and the sugar moiety are separate nucleotidyl elements. This analysis is believed to fully comport with the previous restriction practice in the family of applications to which the present application is a divisional.[1] The analysis also conforms to the prosecution history of a related divisional case.[2], pending U.S. Patent Application Serial No. 08/479,997, also filed on June 7, 1995. **Third**, to extend Broker's chemistry beyond the next phosphate moiety of the penultimate nucleotide to which the now oxidized and obliterated former sugar moiety is attached, could lead to arguments *reductio ad absurdum* in the sense that an infringer could freely pick and choose any element upstream as a means for mischaracterizing Applicants' claimed invention or the prior art, or both. Surely, some rule of reason must be applied, particularly in this instance, where the Patent Office has already determined that labeled nucleotidyl phosphates represent a different invention from labeled nucleotidyl bases and labeled nucleotidyl sugars. Thus, the Examiner's characterization of Broker et al. is believed to be appropriate and reasonable with respect to 3' terminal labeling being viewed as phosphate moiety labeling of the penultimate nucleotide in tRNA - and not as the sugar moiety of the penultimate ribonucleotide.

In light of the amendments to claims 1298, 1582, 1705 and 1711 which affect the claims dependent therefrom and the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under §102(b).

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[1] The present divisional application is believed to have evolved out of various restriction requirements in predecessor applications. Evidently, the Patent Office had required restriction or had agreed to restricting Applicants' originally filed claimeds to several inventions, including separate inventions for base labeled nucleotides, sugar labeled nucleotides and phosphate labeled nucleotides. Divisional applications were subsequently filed for base labeled nucleotides, sugar labeled nucleotides and phosphate labeled nucleotides.

[2] In related U.S. Patent Application Serial No. 08/479,997, also filed on June 7, 1995, compositions comprising phosphate moiety labeled nucleotides were recently rejected over another of Dr. Norman Davidson's papers which similarly disclosed the vicinal oxidation chemistry of the presently cited Broker et al. That related divisional application is also pending at this time.

The Rejection Under 35 U.S.C. §103

Claims 1712-1718 and 1727 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Langer et al. ["Enzymatic synthesis of biotin-labeled polynucleotides: Novel nucleic acid affinity probes," Proc. Natl. Acad. Sci. (USA) 78:6633-6637 (1981)] taken in view of Axel et al., U.S. Patent No. 4,399,216 (issued August 16, 1983, based upon an application filed on February 25, 1980). In the Office Action (pages 7-8), the Examiner stated:

> Langer et al. describes the practice of biotin labeling of hybridization probes therein, taken as a whole. Langer et al. suggests and motivates various uses of such non-radioactively labeled probes including in blots in the DISCUSSION section on page 6637. Langer et al. lacks specifics as to blot hybridization practice.
>
> Axel et al. contains a description of a famous type of blot, called a Southern blot in column 19, line 44, through column 20, line 15, wherein agarose gel electrophoresis is utilized to separate nucleic acids by size with detection in this case by radioactive labeling.
>
> Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to have substituted the biotin non-radioactive labeling of Langer et al. in the Axel et al. Southern blot procedure as motivated by Langer et al. for such substitution with a reasonable expectation of success as given in Langer et al. thus resulting in the instant invention practice. It is noted that instant claim 1298 is not limited as to what chemical non-radioactive structure is being practiced therein.

The obviousness rejection is respectfully traversed.

It is respectfully submitted that a reading of Langer et al. taken in view of Axel et al. would not have permitted a person of ordinary skill in the art to have arrived at the presently claimed invention.

As set forth in claim 1712, the invention at hand concerns a process for detecting the presence of a nucleic acid of interest in a sample. The process comprises four steps. First, there are provided or generated (i) one or more detectable non-radioactively labeled oligonucleotides or polynucleotides, each of which comprises a sequence sufficiently complementary to the nucleic acid of interest or to a portion thereof to specifically hybridize therewith. The detectable non-radioactively labeled oligonucleotides or polynucleotides comprise one or more detectable non-radioactively modified or labeled nucleotides or nucleotide

analogues. The latter can be attached to or coupled to or incorporated into DNA or RNA. The detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof. Also provided or generated is (ii) a sample that may contain the nucleic acid of interest. The second step calls for forming in liquid phase hybrids comprising one or more of the detectable non-radioactively labeled oligonucleotides or polynucleotides specifically hybridized with said nucleic acid of interest. The next steps call for separating or resolving in a gel the hybrids which have been formed and detecting non-radioactively the separated or resolved hybrids to detect the presence of the nucleic acid of interest.

Applicants respectfully point out that if the elements of Langer et al. and Axel et al. were to have been combined as suggested in the obviousness rejection, at most, a person of ordinary skill in the art would have arrived at the following procedural steps:

a) Applying the analytes to a gel (in the absence of a probe);
b) Separating or resolving the various analyte species (where no probe/analyte hybrids are present in the gel);
c) Denaturing the analytes in the gel matrix (which would have destroyed any hybrids between analyte and probe if probe had been present);
d) Transferring the resolved analytes to a membrane or filter;
e) Fixing the analytes to the membrane or filter;
f) Hybridizing the membrane or filter with a non-radioactively labeled probe (where the analyte is exposed to a probe for the first time); and
g) Detecting the presence of the analyte/probe hybrid on a membrane or filter.

Steps a) through e) describe the Southern transfer procedure, whereas steps f) and g) are from Langer et al.

In sharp contrast to the cited combination of Langer et al. taken in view of Axel et al., the present invention as defined by claim 1712 describes a process that can be summarized thusly:

a) forming a hybrid between the analyte and a non-radioactively labeled probe in liquid phase (prior to subjecting the analyte/probe hybrid in the mixture to resolution processes in a gel);

b) applying the analyte/probe hybrids in the mixture to a gel;

c) separating or resolving the probe/analyte hybrid; and

d) detecting the presence of the resolved probe/analyte hybrid.

It should not be overlooked that the present invention overcomes several deficiencies in Langer et al. and Axel et al. First, there is no need in the present invention for the transfer and fixation steps otherwise required or disclosed by the combined teachings of Langer et al. and Axel et al. Second, the present invention provides improved kinetics of liquid hybridization which are unexpected when compared to the less efficient hybridization of Langer and Axel's two-phase system. Thirdly, any resolving achieved by combining the Langer and Axel disclosures would only have provide for separation of the target analyte from other species; whereas in the present invention, resolving provides an additional degree or level of separation, namely, the separation of analyte/probe hybrids from other species. Fourthly, the present invention provides a simple yet elegant process for separating probe/hybrids from excess probe which is in stark contrast to the laborious multi-step washings required to carry out the Langer/Axel teachings.

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a), thereby placing all of the claims in condition for allowance.

An early indication of allowability is respectfully sought.

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